Acute Mania and Psychosis in the Context of Primary Adrenal Insufficiency: A Systematic Review of the Literature

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Background: Given the sparse nature of acute mania or psychosis in primary adrenal insufficiency (PAI), physicians may not be aware of the association of these two entities.

Objective: To conduct a systematic review of the literature for the purpose of identifying all studies reporting mania and/or psychosis in individuals with PAI.

Method: We conducted a systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the PubMed, Embase, and Web of Science databases from June 22, 1970 to June 22, 2021, for the purpose of identifying all studies reporting instances of mania or psychosis associated with PAI.

Results: We identified nine case reports featuring nine patients (M_{age} = 43.3 years, male = 44.4%) over eight countries that fit our inclusion/exclusion criteria. Eight (89%) of the patients had experienced psychosis. Manic and/or psychotic symptom resolution was achieved in 100% of the cases, of which steroid replacement therapy was efficacious in seven (78%) cases and was sufficient in six (67%).

Conclusion: Acute mania and psychosis in the context of PAI is a very rare presentation of an already uncommon disease. Resolution of acute psychiatric change is reliably achieved with the correction of underlying adrenal insufficiency.

Key Words: acute mania, adrenal insufficiency, autoimmune adrenalitis, psychosis, treatment

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ECT = electroconvulsive therapy. **PAI** = primary adrenal insufficiency.

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Adrenal insufficiency is a potentially life-threatening disease that can be classified into three etiological subtypes (Spiegel et al, 2017). In *primary* adrenal insufficiency (PAI), the adrenal cortex itself undergoes end-organ failure; in *secondary* and *tertiary* adrenal insufficiency, the cause of the hypocortisolemic state involves pathology of the pituitary gland (secondary) or hypothalamus (tertiary). Case series published as far back as the 1940s have described the presence of psychiatric symptoms in individuals with PAI, with Engel and Margolin in 1942 and Cleghorn in 1951 independently describing a wide range of psychiatric symptoms in several of their patients with PAI.

Adrenal insufficiency is a relatively rare endocrine disorder that most commonly presents in the setting of autoimmune adrenalitis (Charmandari et al, 2014). Autoimmune adrenalitis is the most common cause of PAI, formerly known as Addison disease, in the Western world, with a prevalence of 4 to 11 cases per 100,000 individuals (Munir et al, 2022). In contrast, for individuals in the developing world, tuberculosis is the most common cause of PAI.

Adrenal insufficiency has been associated with a myriad of potential neuropsychiatric manifestations, including acute mania, psychosis, depression, and anxiety (Anglin et al, 2006; Perry, 2015). Although the role of hypercortisolemia in psychiatric conditions and the association between corticosteroids and psychosis has been well documented, there exists a paucity of literature regarding the association between adrenal insufficiency and manic or psychotic syndromes (Farah et al, 2015; Spiegel et al, 2017). Moreover, when reported, these syndromes have generally been associated with secondary adrenal insufficiency (ie, hypopituitarism) because cases of mania or psychosis secondary to PAI are even rarer.

Given the sparse nature of these cases, physicians may not be aware of the association between acute mania or psychosis and PAI. For this reason, we performed a systematic review of the literature to identify all studies reporting acute mania and/or psychosis in individuals with PAI. Here, we provide a summary of the currently available evidence.

METHOD

Search Strategy

We conducted a systematic review according to PRISMA (Preferred Reporting Items for Systematic

Reviews and Meta-Analyses) guidelines (Moher et al, 2009). We searched the PubMed, Embase, and Web of Science databases from June 22, 1970 to June 22, 2021. The following Boolean search was performed: ("mania" OR "psychosis" OR "bipolar") AND ("adrenal insufficiency").

Once we retrieved the citations, we removed any and all duplicates. Two of our investigators (N.J.B. and A.O.) then independently screened the titles and abstracts according to our inclusion and exclusion criteria. During this screening process, J.G. served as the final arbiter with respect to inclusion in the final analysis. After screening, all remaining articles were subject to full-text review for consideration in the final review. References from the articles selected after full-text review were also scrutinized for further relevant studies.

Variables and Inclusion/Exclusion Criteria

Articles were eligible for inclusion if they were

- available in English or as an English translation;
- primary clinical studies reporting cases of acute mania or psychosis in individuals with PAI, with the diagnosis of acute mania or psychosis mentioned by the primary source using standard diagnostic criteria;
- published in or after 1970;
- from a peer reviewed source; and
- fully accessible.

Articles were excluded if they discussed

- steroid-induced psychosis as a result of adrenal insufficiency treatment,
- adrenal insufficiency resulting from autoimmune polyendocrine syndrome type I,
- adrenal insufficiency resulting from adrenoleukodystrophy,
- patients who underwent adrenalectomy,
- patients with a preexisting psychiatric disorder other than depression/anxiety, or
- secondary/tertiary (as opposed to primary) adrenal insufficiency.

We excluded psychiatric conditions other than acute mania and psychosis because of the correlation between corticosteroids and psychosis.

Qualitative Assessment

N.J.B. and A.O. used the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports (Aromataris and Munn, 2020) to assess each study and determine its suitability for inclusion in our review.

RESULTS

Our search yielded 38 studies from PubMed, 60 from Embase, and 21 from Web of Science (Figure 1). Forty-two studies remained after duplicates were removed. Following screening with respect to our inclusion and exclusion criteria, nine studies remained (Abdulla, 2021; Anglin et al, 2006; Farah et al, 2015; Grover et al, 2012; Harper and Earnshaw, 1970; Lever and Stansfeld, 1983; Mattsson, 1974; Munawar et al, 2019; Puzanov et al, 2019). N.J.B. and A.O. assessed the full texts for final study eligibility.

Study Characteristics

All nine studies were case reports, and each report focused on one patient (Table 1). There were eight unique countries of study origin, with two cases coming from India.

Demographics

The mean age of the patients was 43.3 years, with an age range of 20 to 63 years. Patient sex was 44.4% male (n = 4) and 55.6% female (n = 5).

Qualitative Assessment

Results of the risk of bias assessment using the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports are presented in Table 2. Three of the case reports (33.3%) scored 100% *yes* answers, and the remaining six (66.7%) scored 87.5% *yes* answers. These results do not indicate a risk of bias that would necessitate exclusion of any of the studies.

Past Medical History

Approximately 22% of the patients in our review had a history of hypothyroidism (n = 2), 22.2% (n = 2) had a history of depression, and 11.1% had a history of either tuberculosis (n = 1) or diabetes mellitus type I (n = 1). We categorized patients with PAI in conjunction with either hypothyroidism (n = 2) or diabetes mellitus type 1 (n = 1)—a total of 37.5% of the patients (n = 3)—under autoimmune polyendocrine syndrome type II. A subset of these patients had Schmidt syndrome (specifically, hypothyroidism alongside PAI).

Adrenal Insufficiency

Adrenal involvement was 22.2% tuberculous (n = 2), 22.2% autoimmune (n = 2), and 55.6% unspecified PAI (n = 5). The diagnosis of PAI was achieved using expected laboratory value abnormalities such as low serum cortisol and high serum adrenocorticotropic hormone in seven of the nine reports (77.8%), with two of the seven reports making use of further stimulation tests, with either adrenocorticotropic hormone or cosyntropin.

One of the remaining two reports made the diagnosis through a past medical history of invasive tuberculosis, which necessitated an MRI of the patient, which ultimately revealed adrenal calcification (Lever and Stansfeld 1983). The remaining report did not provide any investigatory details regarding an adrenal diagnosis (Grover et al, 2012). In all nine of the reports, laboratory results and imaging findings were correlated to the signs and symptoms of adrenal insufficiency, such as fatigue, hypotension, and hyperpigmentation.

Psychiatric Symptoms

The nine patients' psychiatric symptoms were categorized as 88.9% psychosis (n = 8), of which 25.0% (n = 2) were further categorized as catatonic (Table 3); the remaining 11.1% of patients (n = 1) were categorized as manic, with symptoms including insomnia, talkativeness,

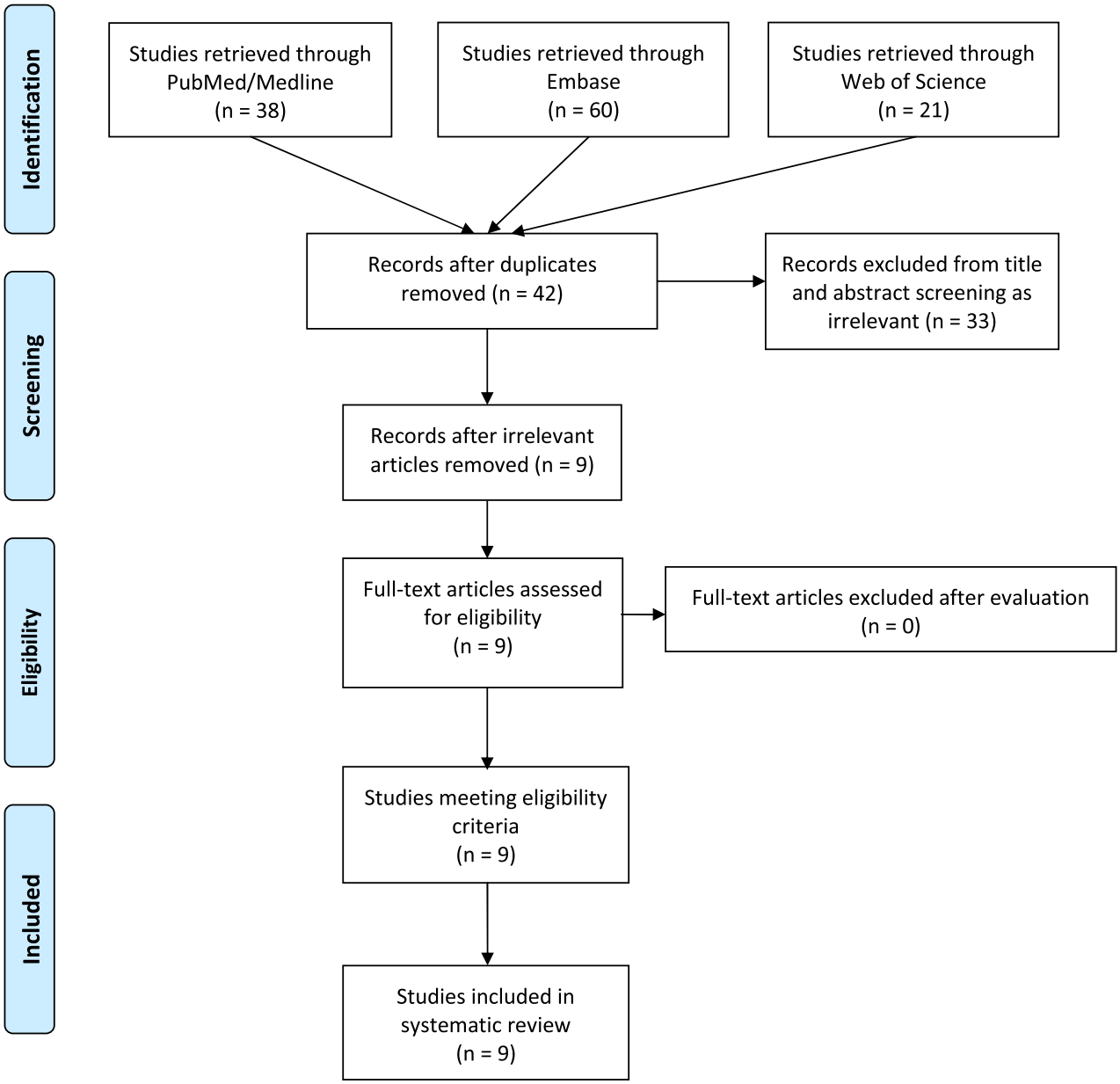

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of our systematic review.

and impulsiveness (Abdulla, 2021). Other medical history (excluding adrenal insufficiency) varied greatly; however, 44.4% of the patients (n = 4) had an unremarkable medical history.

Treatment

In all nine patients, management of adrenal insufficiency (Table 4) was attempted with steroids, often involving the combination of hydrocortisone and fluorohydrocortisone (ie, fludrocortisone). Steroid management led to the resolution of at least one major symptom category in 77.8% of the patients (n = 7) (Abdulla 2021; Anglin et al, 2006; Farah et al, 2015; Harper and Earnshaw, 1970; Mattsson, 1974; Munawar et al, 2019; Puzanov et al, 2019). In addition to hydrocortisone and fluorohydrocortisone, the resolution of persistent catatonic symptoms was attributed to electroconvulsive therapy (ECT) in one patient (Grover et al, 2012).

Antipsychotics (ie, chlorpromazine [n = 2], haloperidol [n = 1], amisulpride [n = 1], and unspecified [n = 1]) were administered in 55.6% of the cases (n = 5), yielding marginal to no improvement of psychiatric symptoms in 80% of these cases (n = 4) (Farah et al, 2015; Grover et al, 2012; Harper and Earnshaw, 1970; Lever and Stansfeld 1983). Benzodiazepines (ie, lorazepam [n = 2] and clopoxid [n = 1]) were administered in 33.3% of the cases (n = 3), including two cases of catatonia (n = 2), yielding no improvement of psychiatric symptoms (Grover

TABLE 1. Study Characteristics

Reference	Study Design	n	Sex	Age	Country	Adrenal Involvement
Harper and Earnshaw (1970)	Case Report	1	F	40	Australia	Autoimmune
Mattsson (1974)	Case Report	1	M	20	Sweden	Autoimmune
Lever and Stansfeld (1983)	Case Report	1	M	53	UK	Tuberculous
Anglin et al (2006)	Case Report	1	F	30	Canada	PAI
Grover et al (2012)	Case Report	1	F	48	India	PAI
Farah et al (2015)	Case Report	1	M	63	Brazil	PAI
Munawar et al (2019)	Case Report	1	F	32	Pakistan	PAI
Puzanov et al (2019)	Case Report	1	F	51	US	PAI
Abdulla (2021)	Case Report	1	M	53	India	Tuberculous

F = female. **M** = male. **PAI** = primary adrenal insufficiency.

et al, 2012; Mattsson, 1974; Puzanov et al, 2019). Additionally, a stimulant, methylphenidate, was administered in one case of catatonia (a trial for akinetic mutism vs catatonia) without symptom resolution (Puzanov et al, 2019).

ECT was attempted in 22.2% of the cases (n = 2). In one case, ECT yielded no improvement of psychosis in the first set of trials and then deterioration of psychotic symptoms in the second set of trials (Mattsson, 1974). In the other case, the catatonic symptoms did not adequately resolve immediately posttherapy, but the patient eventually returned to baseline (Grover et al, 2012). This return may have been attributable to steroid treatment, as ECT was administered alongside fludrocortisone in order to regulate sodium levels.

TABLE 2. Risk of Bias Assessed by the Joanna Briggs Institute for Critical Appraisal Checklist for Case Reports

Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	% Yes
Harper and Earnshaw (1970)	+	+	+	+	+	+	−	+	87.5
Mattsson (1974)	+	+	+	+	+	+	+	+	100
Lever and Stansfeld (1983)	+	+	+	+	+	+	−	+	87.5
Anglin et al (2006)	+	+	+	+	+	+	−	+	87.5
Grover et al (2012)	+	+	+	+	+	+	+	+	100
Farah et al (2015)	+	+	+	+	+	+	−	+	87.5
Munawar et al (2019)	+	+	+	+	+	+	−	+	87.5
Puzanov et al (2019)	+	+	+	+	+	+	+	+	100
Abdulla (2021)	+	+	+	+	+	+	−	+	87.5

Q1: Were the patient's demographic characteristics clearly described? Q2: Was the patient's history clearly described and presented as a time line? Q3: Was the current clinical condition of the patient on presentation clearly described? Q4: Were diagnostic tests or assessment methods and the results clearly described? Q5: Was the intervention(s) or treatment procedure(s) clearly described? Q6: Was the post-intervention clinical condition clearly described? Q7: Were adverse events (harms) or unanticipated events identified and described? Q8: Does the case report provide takeaway lessons? Yes (+), No (−).

Because tuberculous adrenalitis was present in 22.2% of the cases (n = 2) (Abdulla, 2021; Lever and Stansfeld, 1983), management included a combination of rifampicin, isoniazid, pyrazinamide, and ethambutol for tuberculosis treatment in these cases in addition to steroid management. Additionally, because hypothyroidism was present in 22.2% of the cases (n = 2), L-thyroxine was added for treatment in these cases (Anglin et al, 2006; Harper and Earnshaw, 1970). One patient had psychotic symptoms reemerge alongside a new presentation of syndrome of inappropriate antidiuretic hormone secretion after initial resolution with antitubercular and steroid treatment. In this case, the syndrome of inappropriate antidiuretic hormone secretion and subsequent psychosis was corrected with demethylchlortetracycline (Lever and Stansfeld, 1983).

Clinical Outcome

In every case report included in our systematic review, either the patient's acute manic and/or psychotic episode was completely corrected or a return to baseline was achieved (Table 4). There were three studies that included follow-up, ranging from 2 months to 2 years (Anglin et al, 2006; Harper and Earnshaw, 1970; Lever and Stansfeld, 1983). There were no instances of relapse in two of the cases and one 24-hour relapse in the study with 2 years of follow-up (Lever and Stansfeld, 1983). This patient had two other instances of relapse in the case report; none of the other eight patients included in our review experienced a relapse during the time specified in their respective case reports.

DISCUSSION

In our systematic review, we found nine cases of acute mania or psychosis in patients with PAI. The diagnosis was mostly achieved through laboratory abnormalities correlated with signs and symptoms of adrenal insufficiency in the context of acute mania and psychosis. The treatment course typically involved addressing the underlying adrenal crisis with a variety of gluco- or mineralocorticoids, with a few case reports describing the use of primary psychiatric intervention in the form of antipsychotic medication or even ECT. Ultimately, all of the

TABLE 3. Psychiatric Symptoms Experienced by Included Patients

Reference	Sex	Age	Psychiatric Symptom
Harper and Earnshaw (1970)	F	40	Psychosis, delirium
Mattsson (1974)	M	20	Psychosis (delusions), anxiety, delayed thought process
Lever and Stansfeld (1983)	M	53	Psychosis (delusions, hallucinations)
Anglin et al (2006)	F	30	Psychosis (delusions), agitations, aggression
Grover et al (2012)	F	48	Psychosis, catatonia
Farah et al (2015)	M	63	Psychosis (delusions), paranoia, infantile speech
Munawar et al (2019)	F	32	Psychosis, slurred speech
Puzanov et al (2019)	F	51	Psychosis, catatonia
Abdulla (2021)	M	53	Mania (insomnia, talkativeness, impulsiveness)

F = female. **M** = male.

patients achieved psychiatric symptom resolution or a return to baseline.

Mechanism of Neuropsychiatric Symptoms

Although the exact mechanism responsible for the development of neuropsychiatric manifestations in patients with adrenal insufficiency remains unclear, researchers have hypothesized that the up-regulation and sensitization of gluco- and mineralocorticoid receptors in the hippocampus in the context of deficient corticosteroid levels may be at least partially responsible (Berardelli et al, 2016; Farah et al, 2015; Herman et al, 2016; Holtzman et al, 2013; Jacobson and Sapolsky, 1991; Prigent et al, 2004). Decreased glucocorticoid activation has also been associated with impaired prefrontal cortical cognitive function.

Similarly, hyponatremia caused by adrenal insufficiency could alter one's memory, thinking, and consciousness secondary to brain swelling and an encephalopathic state (Charmandari et al, 2014). Another hypothesis explores the possibility of an elevated endorphin state in the body linked to the appearance of psychiatric symptoms because endorphins have been linked to the pathogenesis of psychosis (Amir et al, 1981). An elevated proopiomelanocortin, the pituitary-produced precursor to adrenocorticotropin hormone, melanocyte-stimulating hormone, and beta-endorphin, is typically present in individuals with PAI; therefore, elevated beta-endorphin levels may be present in the body (Holtzman et al, 2013; Johnstone et al, 1990).

Types of Neuropsychiatric Symptoms

Although psychiatric symptoms are associated with PAI, the most common being depression, they are rarely seen in the absence of the classic somatic symptoms such as fatigue, nausea, and salt craving, among others (Bancos et al, 2015; Farah et al, 2015; Thomsen et al, 2007). Indeed, only one (11.1%) included report by Farah et al (2015) described psychosis as the only manifestation of confirmed PAI. When seen in patients with PAI, the variety of psychiatric symptoms intensify in parallel with the extent of adrenal involvement (Farah et al, 2015).

Due to the narrowed symptom selection criteria of the present review including only patients with mania or related psychoses, the correlation of psychoses with adrenal involvement is difficult to measure. Notwithstanding the homogeneity in symptom severity, an increased rate of relapse was seen in the patient with a history of progressively invasive tubercular adrenal involvement (Lever and Stansfeld, 1983). Tubercular involvement has also been noted in a patient who developed organic delusional disorder, with a similarly challenging symptom profile of recurrent delusions, vomiting, and giddiness (Govind et al, 2022).

Diagnosing Adrenal Insufficiency

When acute psychiatric change is seen in individuals with PAI, securing a diagnosis of PAI can be challenging due to a strong consideration for primary psychiatric disease. One cross-sectional study by Bleicken et al (2010) (N = 84) stated that an initial false diagnosis occurred in 84% of their patients with PAI (n = 74), in which a diagnosis of psychotic and psychiatric diseases was wrongly attributed 50% of the time (Engel and Margolin 1942). Our systematic review found only one instance where primary psychiatric disorder was assumed and treated before adrenal insufficiency (Grover et al, 2012). However, the patient cohort in our review was biased toward hospitalized patients, who, irrespective of presenting symptoms, are subject to routine metabolic and hematologic testing. Such testing will likely reveal metabolic derangement in these patients, such as the characteristic hyponatremia, which often prompts an investigation into adrenal insufficiency—as it often did in the included case reports. Nevertheless, PAI can present with normal electrolytes in 20–30% of patients, which may be the ideal cohort of patients wherein a primary psychiatric misdiagnosis occurs (Bancos et al, 2015). However, the only patient in our review who presented with normal electrolytes

TABLE 4. Course of Treatment and Corresponding Clinical Efficacy for Included Patients

Reference	Sex	Age	Treatment Course	Efficacy
Harper and Earnshaw (1970)	F	40	Chlorpromazine 10 mg 3× daily	Discontinued due to syncope
			L-thyroxine 0.1 mg 3× daily	
			Fluorohydrocortisone 0.1 mg daily	Corrected psychosis
			Cortisone acetate 12.5 mg 3× daily, and above L-thyroxine, fluorohydrocortisone	Symptom free at 6-month reassessment with no relapse event
Mattsson (1974)	M	20	Cortisone 50 mg, daily for 1 month	
			Fluorohydrocortisone 0.1 mg, daily for 1 month	Corrected somatic symptoms but psychosis persisted
			Clopoxid 30 mg, daily for 1 month	No improvement
			Electroconvulsive therapy	Deterioration in psychosis
			Haloperidol 2 mg daily for 2 weeks	Corrected psychosis
Lever and Stansfeld (1983)	M	53	Hydrocortisone 30 mg, 5 days	
			Fludrocortisone 0.1 mg, 5 days	
			Rifampicin, isoniazid, pyrazinamide, ethambutol	Corrected psychosis, relapse 5 days later
			Chlorpromazine 50 mg 3× daily for 10 days, then	
			Demethylchlortetracycline 300 mg, 4× daily for 4 days	Corrected psychosis, relapse 15 weeks later
			Trifluoperazine 5 mg 2× daily	Corrected psychosis, one 24-hour relapse over 2 years follow-up
Anglin et al (2006)	F	30	Hydrocortisone for 10 days	
			Fludrocortisone for 3 days	Corrected psychosis
			L-thyroxine and above hydrocortisone, fludrocortisone on discharge	Symptom free at 2-month reassessment with no relapse event
Grover et al (2012)	F	48	Amisulpride 100 mg	No improvement
			Lorazepam up to 12 mg	No improvement in catatonia
			Hydrocortisone	No improvement
			Fludrocortisone 0.5 mcg, 1× daily	
			Electroconvulsive therapy	Return to baseline after 6 trials
Farah et al (2015)	M	63	Antipsychotic medication trial	No improvement in psychosis
			Hydrocortisone IV for 3 days	Corrected psychosis
			Prednisone on discharge	
Munawar et al (2019)	F	32	Hydrocortisone IV for 2 days	Corrected psychosis
			Methylprednisolone 10 mg daily and 5 mg evening on discharge	
Puzanov et al (2019)	F	51	Lorazapam 2-mg challenge	No improvement in catatonia
			Methylphenidate 10 mg, 2× daily	No improvement in catatonia
			Hydrocortisone 20 mg daily and 10 mg evening	Improvement in mental status
			Fludrocortisone 50 mcg added to hydrocortisone	Return to baseline
Abdulla (2021)	M	53	Hydrocortisone 50-mg IV, 4× daily for 1 week	
			Rifampicin, isoniazid, pyrazinamide, ethambutol quad therapy for TB	Corrected psychosis

F = female. **M** = male. **TB** = tuberculosis.

endorsed PAI as past medical history, which was then confirmed with laboratory workup (Munawar et al, 2019).

Treating Adrenal Insufficiency

In 77.8% of the cases (n = 7) included in our review, steroid management was able to resolve at least one component of the patients' manic/psychotic symptoms by correcting the underlying adrenal insufficiency. However, in two cases with steroid management, the steroids were unable to resolve the psychiatric symptoms present despite successful correction of the patients' somatic symptoms (Grover et al, 2012; Mattsson, 1974). In these two cases, ECT and haloperidol were effective at resolving the catatonic and psychotic symptoms, respectively.

Although antipsychotics such as haloperidol do not correct adrenal insufficiency, haloperidol was effective in one case in which steroid management was insufficient and the patient also had elevated homovanillic acid levels (Mattsson, 1974). This relationship between psychosis and high dopamine levels has been historically supported by the *dopamine hypothesis*, which dates back to 1966 when van Rossum proposed that psychosis could be caused by overstimulation of dopamine receptors (Tost et al, 2010; van Rossum, 1966). Taken on the whole, treatment of the underlying condition, whose severity parallels the severity of psychiatric derangement (Farah et al, 2015), was very effective for addressing these derangements given all of the patients were resolved as symptom free or back to baseline, and seven of nine achieved this outcome with steroid therapy alone (six) or in combination with antipsychotics (one).

Other Considerations

Patients with autoimmune polyendocrine syndrome type I were excluded from our review, and although PAI shares many of the same clinical characteristics, autoimmune polyendocrine syndrome type I typically leads to a myriad of severe autoimmune disorders due to an autoimmune dysregulation via mutations in autoimmune suppressor genes (Eisenbarth and Gottlieb, 2004). Similarly, patients with adrenoleukodystrophy were excluded despite its adrenal gland involvement and similar psychiatric association due to its severe demyelinating nature and multisystem symptomatology (James et al, 1984; Kemp et al, 2016; Kopala et al, 2000; Ramos-Ríos et al, 2009). However, patients with autoimmune polyendocrine syndrome type II were included in the review because type II is more common than type I, and patients with type II present with common to intermediately prevalent diseases such as hypothyroidism and diabetes mellitus type I, respectively, alongside PAI (Eisenbarth and Gottlieb, 2004).

Study Limitations

Although we adhered to the recommended guidelines for performing a comprehensive literature search and thorough data collection, we acknowledge several limitations to the present study. Due to the rarity of acute mania and psychosis in individuals with PAI, we were able to identify only nine case reports that fit the inclusion criteria, which limits the power of our review. Only case reports were identified, and there was a large heterogeneity between the reported clinical variables across studies. Additionally, it is difficult to distinguish PAI from a more encompassing autoimmune disorder that could complicate management and account for varying clinical presentations. Because PAI is considered a rare disorder, it also becomes very likely that affected patients will concomitantly suffer from other diseases or develop them in the future (Eisenbarth and Gottlieb, 2004).

Our review included patients who could potentially be, or were, formally diagnosed with autoimmune polyendocrine syndrome type II, including the combination of PAI and either hypothyroidism (n = 2) or diabetes mellitus type I (n = 1). Notably, steroid management was successful in treating the psychotic symptoms in all three of these cases.

CONCLUSION

Acute mania and psychosis in the context of PAI is a very rare presentation of an already uncommon disease. Despite the rarity of PAI, it is imperative for health care professionals to consider a diagnosis of PAI when patients present with typically uncharacteristic psychiatric symptoms such as acute mania and psychosis, especially alongside the classical symptoms of adrenal insufficiency, such as fatigue, weakness, nausea, vomiting, salt craving, and others. Although diagnosis, and subsequent treatment, of PAI can be obfuscated by acute psychiatric changes, a patient's psychiatric prognosis is excellent when the underlying adrenal insufficiency is ultimately diagnosed and corrected with steroid replacement.

REFERENCES

Abdulla MC. 2021. Reversible cerebellar ataxia and bipolar disorder secondary to tuberculous adrenalitis. *Int J Mycobacteriol*. 10:79–81. doi:10.4103/ijmy.ijmy_201_20

Amir S, Amit Z, Brown ZW. 1981. Stress, endorphins and psychosis. a hypothesis. *Mod Probl Pharmacopsychiatry*. 17:192–201. doi:10.1159/000402415

Anglin RE, Rosebush PI, Mazurek MF. 2006. The neuropsychiatric profile of Addison's disease: revisiting a forgotten phenomenon. *J Neuropsychiatry Clin Neurosci*. 18:450–459. doi:10.1176/jnp.2006.18.4.450

Aromataris E, Munn Z. 2020. *JBI Manual for Evidence Synthesis*. Adelaide, Australia: JBI10.46658/JBIMES-20-01

Bancos I, Hahner S, Tomlinson J, et al. 2015. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol*. 3:216–326. doi:10.1016/S2213-8587(14)70142-1

Berardelli R, Karamouzis I, D'Angelo V, et al. 2016. The acute effect of a mineralocorticoid receptor agonist on corticotrope secretion in Addison's disease. *J Endocrinol Invest*. 39:537–542. doi:10.1007/s40618-015-0393-5

Bleicken B, Hahner S, Ventz M, et al. 2010. Delayed diagnosis of adrenal insufficiency is common: a cross-sectional study in 216 patients. *Am J Med Sci*. 339:525–531. doi:10.1097/MAJ.0b013e3181db6b7a

Charmandari E, Nicolaides NC, Chrousos GP. 2014. Adrenal insufficiency. *Lancet*. 383:2152–2167. doi:10.1016/S0140-6736(13)61684-0

Cleghorn RA. 1951. Adrenal cortical insufficiency: psychological and neurological observations. *Can Med Assoc J*. 65:449–454.

Eisenbarth GS, Gottlieb PA. 2004. Autoimmune polyendocrine syndromes. *N Engl J Med*. 350:2068–2079. doi:10.1056/NEJMra030158

Engel GL, Margolin SG. 1942. Neuropsychiatric disturbances in internal disease: metabolic factors and electroencephalographic correlations.

Arch Intern Med (Chic). 70:236–259. doi:10.1001/archinte.1942.00200200056004
Farah JDL, Lauand CV, Chequi L, et al. 2015. Severe psychotic disorder as the main manifestation of adrenal insufficiency. *Case Rep Psychiatry*. 2015:512430. doi:10.1155/2015/512430
Govind P, Subramanian K, Kumar S. 2022. Diagnostic and therapeutic implications of organic delusional disorder due to tuberculous adrenalitis. *Case Rep Psychiatry*. 2022:5056976. doi:10.1155/2022/5056976
Grover S, Girigowda VK, Aggarwal M, et al. 2012. Catatonia associated with hyponatremia treated with electroconvulsive therapy. *J ECT*. 28: e33–e34. doi:10.1097/YCT.0b013e3182545192
Harper MA, Earnshaw BA. 1970. Combined adrenal and thyroid deficiency (Schmidt's syndrome) presenting as an acute psychosis. *Med J Aust*. 1:546–548. doi:10.5694/j.1326-5377.1970.tb78043.x
Herman JP, McKlveen JM, Ghosal S, et al. 2016. Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr Physiol*. 6:603–621. doi:10.1002/cphy.c150015
Holtzman CW, Trotman HD, Goulding SM, et al. 2013. Stress and neurodevelopmental processes in the emergence of psychosis. *Neuroscience*. 249:172–191. doi:10.1016/j.neuroscience.2012.12.017
Jacobson L, Sapolsky R. 1991. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocr Rev*. 12:118–134. doi:10.1210/edrv-12-2-118
James AC, Kaplan P, Lees A, et al. 1984. Schizophreniform psychosis and adrenomyeloneuropathy. *J R Soc Med*. 77:882–884. doi:10.1177/014107688407701015
Johnstone PA, Rundell JR, Esposito M. 1990. Mental status changes of Addison's disease. *Psychosomatics*. 31:103–107. doi:10.1016/S0033-3182(90)72226-8
Kemp S, Huffnagel IC, Linthorst GE, et al. 2016. Adrenoleukodystrophy—neuroendocrine pathogenesis and redefinition of natural history. *Nat Rev Endocrinol*. 12:606–615. doi:10.1038/nrendo.2016.90
Kopala LC, Tan S, Shea C, et al. 2000. Adrenoleukodystrophy associated with psychosis. *Schizophr Res*. 45:263–265.
Lever EG, Stansfeld SA. 1983. Addison's disease, psychosis, and the syndrome of inappropriate secretion of antidiuretic hormone. *Br J Psychiatry*. 143:406–410. doi:10.1192/bjp.143.4.406
Mattsson B. 1974. Addison's disease and psychosis. *Acta Psychiatr Scand*. 50:203–210. doi:10.1111/j.1600-0447.1974.tb08908.x
Moher D, Liberati A, Tetzlaff J, et al. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 6:e1000097. doi:10.1371/journal.pmed.1000097
Munawar M, Iftikhar PM, Hasan CA, et al. 2019. Neuropsychiatric manifestation of Addison's disease: a rare case report. *Cureus*. 11: e4356. doi:10.7759/cureus.4356
Munir S, Quintanilla Rodriguez BS, Waseem M. 2022. Addison Disease. *StatPearls*. Treasure Island, Florida: StatPearls.
Perry BI. 2015. A psychiatric presentation of adrenal insufficiency: a case report. *Prim Care Companion CNS Disord*. 17:10.4088/PCC.15l01819. doi:10.4088/PCC.15l01819
Prigent H, Maxime V, Annane D. 2004. Science review: mechanisms of impaired adrenal function in sepsis and molecular actions of glucocorticoids. *Crit Care*. 8:243–252. doi:10.1186/cc2878
Puzanov M, Davis H, Holmes EG. 2019. A rare presentation of catatonia due to primary adrenal insufficiency. *Psychosomatics*. 60:630–633. doi:10.1016/j.psym.2019.02.008
Ramos-Ríos R, Berdullas J, Araúxo A, et al. 2009. Schizophreniform psychosis at onset of adrenoleukodystrophy. *CNS Spectr*. 14: 711–712. doi:10.1017/s109285290002397x
Spiegel DR, Nelson AB, Lieb DC, et al. 2017. A case of psychosis in a patient with secondary adrenal insufficiency: a possible etiological role of a hypocortisolemic-induced increase in proinflammatory cytokines. *Innov Clin Neurosci*. 14:4–10.
Thomsen AF, Kvist TK, Andersen PK, et al. 2007. The risk of affective disorders among patients with adrenocortical insufficiency: secondary publication. *Ugeskr Laeger*. 169:1473–1475. doi:10.1016/j.psyneuen.2006.01.003
Tost H, Alam T, Meyer-Lindenberg A. 2010. Dopamine and psychosis: theory, pathomechanisms and intermediate phenotypes. *Neurosci Biobehav Rev*. 34:689–700. doi:10.1016/j.neubiorev.2009.06.005
van Rossum JM. 1966. The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Arch Int Pharmacodyn Ther*. 160:492–494.